REMARKS

Reconsideration of the claims in view of the Amendment and Remarks is requested.

Claims 1-3, 7-8, 10-12, 20, 22-23 have been amended. Claims 1, 20, and 23 have been amended to clarify the claims. Claims 2-3, 7-8, 10-12, and 22 have been amended to correct claim dependencies and provide antecedent basis. The amendments to the claims are supported throughout the specification including at page 3, lines 20-25; page 10, lines 2-3; page 10, lines 25-28; page 25, lines 35-36; and page 29, lines 13-15.

Claims 9 and 21 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in one or more continuations applications.

Claims 24-35 are new. The new claims are supported throughout the specification and the originally filed claims

Interview summary

Applicants thank the Examiner Wessendorf for the interview on October 18, 2006. We discussed the 112 rejection and claim amendments that could overcome the rejection. We discussed the 103 rejection. Applicants pointed out that Table 4 in the specification shows that when some amino acids are substituted at the A2 position they do not stabilize the turn sequences, thus, randomly substituting amino acids at this position would not make a tryptophan at this position obvious in view of the cited art.

35 U.S.C. §112, first paragraph

Claims 1-3, 7-12, and 20-23 were rejected under 35 U.S.C. § 112 for lack of written description. Claims 9 and 21 have been cancelled, rendering the rejection of these claims moot. Applicants respectfully traverse this rejection.

The Examiner asserts that the specification provides no kind, length or combination of amino acid residues in the short cyclic peptide that A3 can prossess to exhibit any turns for the peptide. The Examiner also asserts that the specification provides no specific description of a cyclic peptide having additional residues at the N or C terminus.

As an initial matter, Applicants note there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. See

Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph "Written Description Requirement" IIA. Furthermore, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by reduction to practice, by disclosure of relevant identifying characteristics such as structure, physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of these characteristics. *MPEP 2163 II. A.3.(a)ii).* When the above factors are carefully weighed, the specification clearly describes the claimed subject matter in a manner reasonably conveying to one of skill in the art that Applicants had possession of the claimed invention.

Applicants submit that one of skill in the art reading the specification would understand that Applicants were in possession of the claimed cyclic peptides. Applicants have described the structure of the claimed peptides including that of the A3 position. Applicants have described that the A3 position can include up to 8 amino acids and can be any naturally occurring amino acid. Applicants have demonstrated that the claimed cyclic peptide can stabilize a number of different types of reverse turn sequences including different types of β turns. Applicants further describe that other turn sequences having 8 amino acids were known in the art. See the specification at page 29, lines 13-15.

In a specific embodiment, Applicants have demonstrated the preparation of a library of cyclic peptides comprising CX8C as well as XCTWX4LTCX, wherein X4 is any naturally occurring amino acid. See the specification at page 23, Example 1 and page 35, Example 5. Applicants have further described many specific embodiments at page 29 in the specification. Applicants have shown and described that different turn sequences having different amino acid sequences can be presented as cyclic peptides as claimed and that these sequences are presented as stabilized turn sequences. Therefore, Applicants have described the structure of the claimed cyclic peptides, many species of the claimed cyclic peptides, and provide an actual reduction to practice.

Furthermore, the Applicants have in fact disclosed and exemplified a representative number of species within the claimed genus. The disclosure specifically exemplifies a scaffold shown to stabilize the turn sequence EGNK (Example 1), the C'-C" hairpin loop (residues 37-46) of the CD4 region of HIV gp120 (Example 2), the turn sequence ENGK, the turn sequence

QGSF; the turn sequence KGNE; the turn sequence VWQL from the F-G loop of domain 2 of human Fc-epsilon-RI (Example 2), and the turn sequence GPLT from the EPO agonist peptide EMP1 (Example 2). Indeed, the specification discloses that some of these sequences are "difficult" turns, yet were successfully stabilized by the claimed peptide scaffold (page 29, lines 10-12). Therefore, Applicants submit that the specification discloses a representative number of species of the genus of A3.

Applicants also submit that many beta-turn sequences are known in the art, such that the claims need not be limited to peptides comprising turn structures having a specific primary sequence. Applicants submit that a turn sequence is a secondary structure feature and is not dependent on the primary sequence of the turn sequence. Applicants have shown that a cyclic peptide with the flanking residues as claimed provides for presentation of this structural feature in the proper conformation regardless of the primary sequence. Beta turn sequences are a structural feature of proteins that can contribute or participate in biological function, e.g. ligand/receptor interaction. The ability to identify novel peptides comprising beta turn sequences provides the identification of novel therapeutic agents that can affect the biological activity of proteins. One of ordinary skill in the art would readily recognize that the peptides of the invention are useful for stably presenting a variety of turn sequences.

In response, the Examiner contends that the specific disclosed embodiments for position A3 do not adequately describe all possible combinations of residues that can comprise A3. The Examiner asserts one would expect the ability of the claimed peptides to display a known beta turn sequence, but that some peptides are less accommodating to insertions into other peptides.

Applicants, assert, however, that the present claims are not directed to the insertion of a beta turn sequence into any peptide, but rather into a structurally constrained peptide that has been shown to successfully present different types of beta turn sequences, including difficult β turn sequences, as discussed above. The peptides of the claimed libraries include two cysteine residues that are capable of forming a disulfide bond, which facilitates formation of beta hairpin turns. The peptides additionally comprise specified residues A2, A3, A4, and A5, which stabilize beta turn structures (page 9, lines 19-23 of the specification). In particular, positions A2 and A4 are either to W, or to W or L. The specification provides data demonstrating the

discovery of the general ability of trp-trp or trp-leu pairs at these positions to optimally stabilize hairpin turn sequences (see Example 4).

The Examiner has also indicated that Applicants have failed to provide written description of additional amino acids at the N and/or C terminal ends. Applicants submit that it is the structurally constrained cyclic peptide that provides for stabilization and presentation of the turn sequences and that additional amino acid sequences on the N and C terminal ends of the peptide do not affect the conformation of the peptide. Applicants have described the fusion of these peptides with a phage coat protein. Thus, Applicants submit they have described and characterized a library of structurally constrained cyclic peptides, wherein each cyclic peptide has about 1-50 amino acids at N and/or C terminal ends.

Consequently, the Applicants submit that the disclosure of the stabilizing effects of trp-trp and trp-leu pairs, along with the working examples showing the ability of the claimed peptides to successfully display multiple different beta turn sequences, would lead one of ordinary skill to recognize that Applicants have disclosed a representative number of species encompassed by the claims. Applicants assert that the claims are fully described by the specification, and withdrawal of the rejection is therefore requested.

35 U.S.C. §112, first paragraph

Claim 23, as amended, was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that the presence of X1 and X2, each having 1-50 amino acid residues, is confusing because it is unclear how a library can be isolated from a polypeptide containing unidentified residues. Applicants traverse this rejection.

The definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *MPEP 2173.02.*

As disclosed by the specification, in one embodiment of the invention the carboxy and amino terminal ends of peptides of the claimed libraries may be bonded to about 1-50 other amino acid residues through conventional amide peptide bonds, using conventional peptide

synthesis techniques (page 10, lines 30-35). These additional residues may be chosen to be, for example, part of a known protein containing a beta turn, and may be added, for example, to determine the effect of the beta turn structure on the structure of the overall polypeptide or to determine the effect of the additional residues on the binding of the peptide with a protein of interest (page 10, line 35 through page 11, line 2). In addition, the additional amino acid residues may be a viral coat protein for utilization in phage display.

Consequently, since the Applicants submit that one of skill in the art practicing the claimed invention would select the identity of the amino acid residues represented by X1 and X2, and would therefore be readily able to recognize and isolate the peptides of the claimed library, wherein X1 and X2 comprise selected amino acids. As a result, the Applicants submit that the claim is not unclear. Withdrawal of the rejection is requested.

35 U.S.C. §103 (a)

The Examiner rejected claims 1-3, 7-10, and 20-23 under 35 U.S.C. § 103(a) as being unpatentable over Wrighton et al. (U.S. Pat. No. 5,830,851). The Examiner asserts that the peptide libraries of Wrighton et al. render the claimed library *prima facie* obvious, for reasons of record. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met, namely: (1) the reference must teach or suggest all of the claim limitations; (2) there must be a suggestion or motivation, either in the reference itself or in the knowledge generally available to one of skill in the art to modify the reference to obtain all of the claim limitations; and (3) there must be a reasonable expectation of success. Applicants submit that not all of these requirements have been met, because the reference does not disclose all of the claim limitations, there is no suggestion or motivation to modify the reference to disclose all of the claim limitations, and there would not have been a reasonable expectation of success in doing so.

Independent claims 1, 20, and 23 are directed to a structurally-constrained cyclic peptide (claims 1 and 23), or a cyclic peptide having a reverse turn secondary structure (claim 20), wherein the cyclic peptide comprises an amino acid sequence C1-A1-A2-$(A3)_n$-A4-A5-C2, wherein A2 and A4 are W (claim 23), or A2 is 2 and A4 is W or L (claims 1 and 20).

As stated in the previous Response, the Applicants note that Wrighton et al. fails to disclose a single cyclic peptide species within the scope of the claims. Relevant factors that may help to support a showing of *prima facie* obviousness include: 1) the size of the prior art genus, 2) any express teachings in the prior art to select the claimed species or subgenus, 3) any teachings of structural similarity, including any disclosure of typical or preferred species within the disclosed genus, 4) any teachings of similar properties or uses of a structurally similar species by the prior art, 5) the predictability of the technology involved, and 6) any other teachings that would support the selection of the claimed species or subgenus.

Applicants submit that when considered in light of the foregoing factors as discussed below, Wrighton in the least fails to provide any motivation to modify the peptides of Wrighton et al to that of the claimed peptides, such that no prima facie case of prima facie obviousness exists in view of this reference.

Express Teachings of the Prior Art

Applicants submit that Wrighton does not provide any express teachings that would motivate one of ordinary skill to modify the peptides as disclosed in Wrighton to the claimed peptides. Wrighton et al. nowhere teaches or suggests the desirability of forming a trp-trp or trp-leu cross-strand pair between A2 and A4 of the claimed peptides, as a means of enhancing beta turn stability. Wrighton et al. does not teach or suggest the ability of the presently claimed cyclic peptides to accommodate a number of different types of turn structures, or that the stability of the turn sequences would be enhanced by using a cyclic peptide having the presently claimed residues. Indeed, Wrighton et al. fails to teach or suggest the desirability of a peptide that can stabilize a beta turn structure, or even that any peptide can stabilize a beta turn structure.

The Size of the Genus

The Applicants assert that the size of the genus disclosed by the prior art provides further evidence against the obviousness of the present claims. In the present case, the genus disclosed by Wrighton encompasses many more than 20 compounds, such that one of ordinary skill in art could not immediately envisage every species encompassed by the genus. For example, the present claims recite four amino acid residue positions (A1, A2, A4, and A5) that can be varied as part of a scaffold for presenting a sequence A3. A1 and A5 are independently limited to amino acids W, Y, F, H, I, V, or T, A2 is limited to amino acid W, and A4 is limited to amino

acid W or L (claims 1 and 20) or W (claim 23). The Examiner has acknowledged that the corresponding positions of the Wrighton genus, by contrast, may include any of the 20 naturally occurring amino acid residues at each of these 4 positions. Consequently, the Wrighton genus encompasses $20^4 = 160{,}000$ combinations at these 4 positions alone. Therefore, the size of this genus is much greater than the genus at issue in *In re Petering*, and the Applicants respectfully submit that one of ordinary skill in the art could not immediately envisage all of the species of the prior art genus.

The Examiner asserts that since one of ordinary skill would know what each of the 20 natural amino acids are, the combinations representing the peptides of the claims are rendered obvious. Applicants respectfully submit that the Examiner's analysis is improper. In a genus-species context, there must be a motivation to modify the peptides to obtain the particular species or subgenus of the claims from the defined prior art genus. The mere knowledge, by one of ordinary skill, of each amino acid that can be substituted at given positions in accordance with the defined limits disclosed by the prior art for a given genus, cannot render obvious every possible combination that can result from making such substitutions. Indeed, it is for this reason that the MPEP provides guidelines for determining whether a claimed subgenus obvious.

In addition, the Applicants direct the Examiner's attention to Table 4 at page 31 in the specification. Applicants have shown that substitution at the A2 position with, for example, at least val, thr, asp, or ala does not result in stabilization of a β turn sequence. Thus, random substitutions do not teach which amino acids can be substituted at this position and provide for stabilization of the turn sequence. Moreover, applicants submit that the Table shows unexpected results in that tryptophan at the A2 position provides at least a 2.5 or greater increase in stabilization as compared to a leucine at that position or other amino acids at that position. See the specification at page 34, lines 4-9.

Teachings of Structural Similarity

Wrighton et al. specifies that the preferred embodiments have an M, F, or I at the position corresponding to A2. The disclosure of these preferred embodiments would lead one of skill in the art to make different substitutions at this position than those claimed by Applicants, providing further evidence of nonobviousness. The present specification discloses that forming a trp-trp or trp-leu cross-strand pair between A2 and A4 of the claimed peptides can enhance the

stability of a beta turn. None of the preferred embodiments disclosed by the prior art incorporate residues at both A2 and A4 capable of forming a trp-trp or trp-leu cross-strand pair. Such a teaching serves to weigh against a finding of *prima facie* obviousness, by providing a motivation for one of skill in the art to select the preferred species. *MPEP 2144.08II.A(c).* Moreover, other hydrophobic amino acids such as val and alanine do not provide for stabilization of the β turn sequences as shown in table 4 in the specification.

Teachings of Similar Properties or Uses

Applicants note that "it is the properties and utilities that provide real world motivation for a person of ordinary skill to make species structurally similar to those in the prior art." *MPEP 2144.08II.A4(d).* As is stated in the previous Response, however, Wrighton et al., is directed to identifying agonists of EPO, and not to peptides capable of stabilizing a turn sequence. Therefore, the Wrighton et al reference is concerned with solving a different problem than that of the Applicants. Wrighton et al.'s failure to teach any properties or uses of the disclosed peptides that are similar to those of the presently claimed peptides is additional the evidence of nonobviousness of the present claims.

The Examiner states that the present rejection does not rely on an "obvious to try" rationale, because Wrighton et al. discloses specific species in addition to a generic library, and because the case law holds that the selection of a certain combination of compounds from among thousands of compounds disclosed by the prior art, can render claims directed to the selected combination obvious (*Merck & Co. Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ 2d 1843 (Fed. Cir. 1989)). The Applicants disagree with the Examiner's conclusion.

Applicants respectfully submit that *Merck* is inapplicable to the present claims, because the issue in *Merck* revolved around combinations of compounds, and not upon the modifications of those compounds. The prior art in *Merck* was directed to compositions comprising the combination of two compounds selected from two classes of compounds known to be useful as diuretics. The holding in *Merck* merely states that the prior art rendered obvious claims directed to compositions comprising a specific compound from each of the classes of compounds disclosed by the prior art.

Applicants submit that claims 1-2, 4-5, and 8-9 are patentable over Wrighton et al., at least for the foregoing reasons. Withdrawal of the rejection is therefore requested.

Other Teachings of the Prior Art

As discussed in the previous Response, the Examiner has alleged the existence of a motivation to modify Wrighton et al. to obtain a species of Applicants' subgenus, by pointing to specific residues of certain Wrighton et al. species (i.e., SEQ ID NOs 86 and 89) that themselves clearly fall outside the present claim scope. The Examiner alleges that Wrighton et al. discloses generally that any natural amino acid can be used at a position corresponding to A2 of the present claims. The Examiner concludes, therefore, that it would have been within the ordinary skill in the art to use a Trp at position A2.

Applicants respectfully submit that the Examiner is combining residues from different peptides of Wrighton et al. to obtain a species falling within the present claims, but without any motivation or reasonable expectation of success, other than that provided by the Applicants' own specification. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." *MPEP 2142*. Applicants submit that only the present specification, and not the prior art, provides the teaching that the claimed peptides are useful in stabilizing ß-turn structures.

Double Patenting

The Applicants acknowledge the provisional rejection of claims 1-3, 7-12, and 20-23 under the judicially created doctrine of obviousness-type double patenting over claims 1-5, 7, 9-11, 13, and 18-25 of copending Application No. 10/271,343. The Applicants address this rejection upon notice of allowable subject matter.

Request for an Interview

Applicants request an interview with the Examiner. Applicants request that the Examiner contact Applicants representative to resolve any outstanding issues.

SUMMARY

Applicants submit that all pending claims are in condition for allowance, and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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